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An update: Health economics of managing multiple myeloma

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ABSTRACT

Based on Medline search, a summary is provided of recent health economic evidence in published literature relating to the management of multiple myeloma. The following major components of current multiple myeloma treatments are discussed: induction chemotherapy, high-dose chemotherapy supported by autologous peripheral stem cell transplantation (ASCT), long-term biphosphonates therapy to prevent skeletal events and recent advances for the treatment of relapsed or refractory multiple myeloma and under evaluation in primary treatment (thalidomide and bortezomib). Our study shows that there still appears to be a need for health economic information to confirm the cost-effectiveness of stem cell support versus high-dose chemotherapy without stem cell support, as well as to assess optimal biphosphonate treatment regimens. There is also a clear need for peer reviewed economic evaluations of novel therapies such as thalidomide and Bortezomib in the treatment of multiple myeloma at different stages of the disease.

1. Introduction

A lot of progress has been achieved in the last decades in the treatment of multiple myeloma. The use of high-dose chemotherapy with stem cell support has clearly improved disease-free survival and has increased overall survival compared to the standard conventional chemotherapy regimen which consisted of melphalan + prednisone for years.[1]

Patients' quality of life has improved since the introduction of biphosphonates as long-term treatments preventing skeletal events which lead to bone pain, mobility loss and treatment requirements.[2]

Lately, new promising agents have been discovered with improved response rates, progression-free and potentially overall survival in different stages of multiple myeloma (newly diagnosed myeloma up to relapsed or refractory disease).[3–5] The acquisition costs of these novel therapies are however very high compared to some established treatments such as corticosteroids,[6] highlighting the need to weigh their benefits against these costs.

In the current health care environment, safety and efficacy are still the primary but no longer the only parameters evaluated to assess the value of treatments. Costs and cost-effectiveness or cost-utility are becoming more important. Increasingly, health care systems are demanding health economic information as part of reimbursement submissions for new therapies.

For therapies introduced prior to this era of economic awareness in health care, economic evaluations are often either lacking, or facing methodological difficulties due to the limited availability of data and the need for extrapolations, which are or can be subject to assumptions.

The purpose of this article is to provide an overview of health economic evidence relating to treatments in multiple myeloma. A similar review was published in 1999[1] and therefore, the current assessment has concentrated on more recently published evaluations.

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2. Materials and methods

A literature search was performed in August 2005 in Medline using the following MeSH terms: multiple myeloma and "cost or pharmacoeconomics". A comprehensive review on pharmacoeconomic literature data with regard to multiple myeloma was published by Wisløff in 1999.[1] In the current paper, we have summarised the findings of Wisløff and have described more recently published papers on the subject of health economics in multiple myeloma management. We have subsequently discussed six different aspects of disease and treatment continuum: non-myeloablative induction chemotherapy, high-dose chemotherapy with stem cell support, allogeneic bone marrow transplantation, interferon-α maintenance, biphosphonates, and "new" technologies.

3. Results

3.1. Non-myeloablative induction chemotherapy

No pharmacoeconomic analyses have been performed on the different therapeutic options for induction chemotherapy. The classical therapy available since the late 1960s consisted of a combination therapy with melphalan and prednisone.[7] This regimen is relatively cheap with low toxicity and significantly improves quality of life in responders. With this conventional chemotherapy, median survival is around 30–36 months and 10 year survival rates are below 5%.[7] A meta-analysis of 27 trials showed no consistent benefit in overall survival with any combination regimen over melphalan + prednisone but findings have suggested that melphalan and prednisone has more favourable effects in good prognosis patients whereas combination chemotherapy seemed preferable in bad prognosis patients. An important drawback of long-term use of alkylating agents such as melphalan, is that they impair stem cell harvest and engraftment.[8–10] With the availability and positive results of high-dose chemotherapy with stem cell support, basic induction therapy with melphalan and prednisone can nowadays be recommended in patients ineligible for transplantation.[1]

Widely applied regimens to date as induction treatment include Melphalan + prednisone or 2–4 cycles of VAD (vincristine + adriamycin + dexamethasone). Although VAD was not shown to have a survival advantage versus melphalan + prednisone, it incurs faster response, and high response rates. It is prescribed in cases with planned ASCT or cases requiring rapid response.[1] Coutet and colleagues have shown that cost containment from outpatient administration of the VAD regimen could provide savings of approximately €3306 or 32% per patient. Facilities and training are of course required to develop an ambulatory chemotherapy administration.[11] Although VAD has been widely applied as induction therapy, peripheral blood stem cells are better mobilised with other regimens such as IEV (Iphosphamide, Etoposide, Doxorubicin), CEV (Cyclophosphamide, Etoposide, Doxorubicin) or cyclophosphamide alone.[12] In addition, the use of VAD is decreasing since response rates are comparable with dexamethasone alone and VAD treatment is more demanding, both from a clinical as from an economic point of view: it requires a central line, inpatient treatment and is associated with important chemotherapy induced toxicity such as neutropenia and thrombocytopenia.[12]

3.2. High-dose chemotherapy with stem cell support

Since the 1980s, clinical evidence has increased and high-dose chemotherapy supported by bone marrow or peripheral blood stem cell transplantation as first-line treatment of multiple myeloma has been suggested to increase survival versus conventional chemotherapy by 1–3 years.[12] A recent meta-analysis showed only a trend toward a long-term survival benefit of high-dose therapy + ASCT (autologous peripheral stem cell transplantation) over conventional therapy for first-line treatment of myeloma. Nevertheless, a clearly delayed time to relapse was reported, with a resulting 14.5 months benefit in mean TWiST (time without symptoms and toxicity).[12,13] Today, long-term remission beyond 7 years can be achieved in respectively 10 and 20% of patients receiving single or tandem ASCT and in 20% of patients receiving allogeneic SCT.[12] A number of modifications have been implemented to transplantation over time to improve clinical efficacy or to simplify procedures and reduce costs. Most of the advances have been associated with cost increases but some have managed to decrease financial burden.[14,15] One of the most important changes in transplantation practice with both cost and clinical benefits consisted of the use of growth factor mobilised peripheral blood stem cells as opposed to bone marrow. Faster recovery of the peripheral blood cell count, decreased procedure related morbidity and mortality and shorter duration of hospital stay compared to the use of bone marrow cells have led to the widespread use of HDC with PBSC support.[16] These advantages brought about a cost decrease which has been reported around US$10000 per treatment[17] or between 27.5% and 44% (Uyl-De Groot, and Duncan in Ref. [1]). It has been shown that the use of growth factors after stem cell reinfusion also enhances neutrophil recovery. Although the clinical benefit was relatively modest, most centres have routinely introduced this practice.[1] On the other hand, the use of total body irradiation (TBI) has been largely abolished in the conditioning prior to stem cell infusion since it adds to toxicity without improving clinical results.[1] TBI also contributed to costs, constituting 7.7% of total costs.[18]

Cost estimates for autologous stem cell support have ranged between US$ 20000 and US$ 80000.[1,16,7] Comparison of the different analyses is difficult due to differences in time horizon, type of costs included and practices considered (use of IFN, choice of conditioning regimen such as melphalan alone, melphalan + TBI, busulphan/cyclophosamide or busulphan + melphalan), perspective taken, country and year of analysis. Table 1 shows an overview of ASCT costs published since 1999.

Another cost saving adaptation shown feasible by Jaganath consists of the ambulatory performance of autotransplants. This has been associated with cost decreases of approximately 40%. Obviously not all patients will be eligible for this procedure depending on their global performance status, educational and social status (Jaganath in Ref. [1]).

Although transplantation today can not be considered as a curative treatment for multiple myeloma, it can be concluded that there is a prolongation in event-free survival and overall

Table 1 – Overview of cost and cost-effectiveness analyses in multiple myeloma since Wisloff[1]

	Mishra	Mishra	Kouroukis	Van Agthoven	Gulbrandsen
Publication year	2005	2003	2003	2004	2001
Country	N	N	Canada	NL	N
Currency	USD	USD	Can $	€	USD
Time horizon	PSCT	PSCT	90mo	36 mo	36 mo
Cost disc (%)	NA	NA	0% (3–5 SA)	4%	5%
Effect disc (%)	NA	NA	0% (3–5 SA)	4%	0%
Analysis	CA	CA	CEA	CUA	CUA
Comparators	NA	NA	MP	Intensive chemo	MP
Sources	Consec pts	Consec pts	Rand trial + historical ctrl	Phase III study (HOVON)	Population study (Nordic Myeloma group)
Perspective	hosp	Hosp	payers	hosp (+amb drugs)	societal
Direct costs	√	√	√	√	√
Indirect costs	√	√	√	–	√
Productivity costs	–	–	–	–	√
IFN	–	–	–	√	√
TBI	–	–	√	√	–
Amb costs	–	–	√	–	√
Total costs	32160 US$	38186 US$	32320 Can$ vs 1803 Can$	80630 € vs 67563 €	34000 US$ vs 9500 US$ (direct)
Incr cost	NA	NA	30517 Can$	13067 €	direct: 24400 US$ indirect 32300 US$
Incr LYs	NA	NA	1.61	−0.14	1.5
Incr QALYs				−0.24	0.81
cost/LYG	NA	NA	25710 Can $	−93336 €	–
cost/QALYG	NA	NA	–	54446 €	27000 US$

Abbr. N: Norway; NL: The Netherlands; PSCT peripheral stem cell transplantation; Mo: months; NA: not applicable; disc: discounting; CA: cost analysis; CEA: cost-effectiveness analysis; CUA: cost-utility analysis; MP: Melphalan + prednisolone; consec pts: consecutive patients (real life data); Rand: randomised; ctrl: controls; hosp: hospital perspective, amb: ambulatory; IFN: interferon maintenance; TBI: Total body irradiation; Incr: incremental; LYs: life years; QALYs: quality adjusted life years; LYG: life year gained; QALYG: quality adjusted life year gained Symbols: √: included; – not included.

survival from 18 to 27 months compared to conventional chemotherapy.[19] In addition, long-term remission can be achieved in up to 20% of patients undergoing SCT.[12] Poorer quality of life scores have been reported during the first six months of treatment in intensive chemotherapy patients versus patients on conventional treatment with melphalan and prednisone. Scores are lower for global quality of life, for role and social functioning and there is more appetite loss (Gulbrandsen, 1998 in Ref. [1]). After 12 months, quality of life improves to the level in control patients. Despite this transient decrease in overall quality of life, the intervention is associated with substantial increase in quality adjusted life years (QALYs), given the prolongation of disease-free and overall survival time. Quality adjusted life years are calculated from life expectancy by attributing a correction factor (between 0 and 1) to each life year which represents the patients' valuation of quality of life. Formal evidence of a benefit exists only in patients under the age of 65 (Attal, and Lenhoff, 1998 in Ref. [1]) but the intervention is more and more offered to patients above that age.

Several studies have analysed the cost-effectiveness of high-dose chemotherapy with stem cell support compared to conventional chemotherapy alone. Most have found cost-effectiveness ratios ranging between US$30 000 and US$ 40 000 per QALY gained.[1] More recent analyses have reported incremental cost-effectiveness ratios of US$ 21 000 per life year (LY)[18] and US$ 27 000 per QALY[20] compared to conventional chemotherapy (Table 1).

Although no cost-effectiveness or cost-utility acceptability threshold has officially been identified by any authority and although such a threshold is likely to differ from one health care setting to another, and even from one disease area to another,[21] the ranges reported for the cost-effectiveness and cost-utility of high-dose chemotherapy with stem cell support compared to conventional chemotherapy may generally be regarded as acceptable, especially given the severity of the disease. Yet, the absence of probabilistic sensitivity analysis in those studies makes it difficult to interpret the uncertainty surrounding the results and hence the likelihood of making a "wrong" decision on health economic grounds (i.e. the probability that cost-effectiveness ratios will lay above the threshold of societal willingness to pay).[22]

Recently, a cost-utility analysis was undertaken in The Netherlands comparing intensive chemotherapy alone with intensive chemotherapy followed by myeloablative chemotherapy with autologous stem cell rescue in newly diagnosed multiple myeloma patients aged ⩽65 (stage II/III).[7] The cost-utility analysis was performed alongside a phase III clinical trial. Quality of life was measured in the phase III trial using the EQ-5-D. Utility values were available from the trial for patients responding to the treatment up to a period of 24 months. For the cost-effectiveness analysis with a time horizon of 36 months, the utility levels were assumed to be stable between 24 and 36 months. For non-responders, a correction factor was applied to the age adjusted utility value for the general population. The correction factor (−19.5%) referred to the state of patients with an undefined state following intentionally curative primary therapy. Cost data were calculated from hospital record retrieved resource use from 100 trial patients (hospital perspective including ambulatory

drugs). A time horizon of three years was applied. The main clinical findings of the study after a median follow-up of 33 months were as follows, for intensive versus myeloablative therapy respectively: complete response rates of 13% and 29%, median event-free survival time of 21 and 22 months, median time to progression of 25 and 31 months and median overall survival of 50 and 47 month. At a three year time horizon a cost difference of €13 067 was found and the total discounted (4%) number of QALYs was 1.83 in the intensive chemotherapy only group and 1.57 in the myeloablative treatment group. The lower QALY result in the myeloablative treatment group resulted from significantly lower utility values during the first year of treatment. It was concluded that, applying a fixed time horizon of three years, it may not be cost-effective to perform myeloablative therapy given that it is associated with less QALYs at a higher overall cost. It should be noted that some of the elements of therapy included in the protocol may not anymore be standard care today, such as for example TBI or potentially interferon maintenance treatment. The inclusion of TBI may have negatively influenced cost-utility of the myeloablative treatment group since it increases costs.[7] As reported earlier, previous studies have concluded that the cost-effectiveness ratio of high-dose therapy with stem cell rescue is acceptable given the clinical benefits. These conclusions have all been drawn comparative to conventional chemotherapy. The cost-utility analysis by van Agthoven however did not confirm the favourable cost-effectiveness of myeloablative chemotherapy with stem cell rescue compared to intensive chemotherapy alone.[7] Since this analysis was based on short-term outcomes, the results need to be interpreted with caution and to be confirmed on the basis of longer term results.[7] High-dose chemotherapy is nowadays offered to all patients up to the age of 70 who are in objective response to induction chemotherapy (Ref. [1], and Sirohi, 2000 in Ref. [7]). Short-term analysis suggests that it may not be cost-effective to add myeloablative therapy to this basic intensive regimen.[7]

Important to note with regard to the former analysis is that the time frame of 3 years is not a sufficient time horizon to cover all the benefits of therapies and therefore, in subsequent analyses using longer term data, more favourable cost-utility results may be obtained. Since the time horizon applied in the analysis and the cut-off time to obtain clinical data is very important, updated analyses as longer term clinical data become available should be performed.[7] An updated analysis at five years follow-up has been reported and showed increases in the differences between study arms in terms of event-free survival (8% versus 22%) and time to progression (median 25 versus 32 months). Hence, it is highly likely that from a longer term perspective the cost-effectiveness of myeloablative treatment may be found more favourable.[7] Although the costs in the myeloablative therapy group will remain higher, it may be that after longer follow-up significant benefits in terms of event-free as well as overall survival are documented and that hence, society may be willing to pay for these benefits.

In conclusion, high-dose chemotherapy associated with stem cell support has been reported to be cost-effective when compared to conventional chemotherapy, however compared to intensive chemotherapy without myeloablative therapy, long-term utility and survival data are required to assess whether the additional costs and the short-term unfavourable effect of myeloablative treatment on quality of life are offset by long-term benefits in terms of event-free and overall survival.

3.3. *Allogeneic bone marrow transplantation*

Allogeneic bone marrow transplantation in multiple myeloma is a potentially curative treatment. It has been shown to induce higher rates of complete response between 30% and 50%, and long-term progression-free survival in 20–55% of patients after myeloablative dose conditioning.[23] However the intervention is associated with higher procedure related mortality. In addition, retrospective multivariate analysis reported similar clinical outcomes to autologous stem cell transplantation.

Until recently, allogeneic transplantations were reserved for rare cases below the age of 40–45.[1] Recent advances, such as intensity-reduced conditioning, aiming at reducing procedure-related toxicity and mortality, have broadened the indication for allogeneic transplantation to older patients.[23,24]

3.4. *Interferon-α maintenance*

Interferon-α has been extensively studied in multiple myeloma with variable reported outcomes, some studies suggest an increased response rate and duration of event-free survival whereas other studies failed to confirm the clinical benefit.[25] Due to the variability in clinical findings in individual studies related to the use of interferon-α, the Myeloma Trialists Collaborative Group performed an individual patient data meta-analysis including 4012 patients. It was found that progression-free survival improved; with most papers reporting a progression-free survival benefit around seven to nine months and individual cases potentially showing much longer benefits; but overall survival benefit, if any, was small and needs to be balanced against the cost and toxicity.[25] The clinical and health economic data available at the time did not firmly support the recommendation of interferon therapy in multiple myeloma. It is important to consider the potential impact of interferon treatment on quality of life. In fact during the first year of treatment, interferon has been reported to reduce quality of life. Assuming treatment as of chemotherapy induction, conservative cost-utility estimates have reported levels generally beyond acceptable thresholds (50 000–100 000 $/QALY).[1] Hence it has been concluded that maintenance treatment with Interferon-α has a modest survival and progression-free survival benefit but due to its cost and toxicity profile it is associated with unfavourable cost-utility ratios.[1] To our knowledge, no health economic assessments have been published more recently.

3.5. *Biphosphonates*

Multiple myeloma is typically characterised by the presence of multiple lytic bone lesions or diffuse osteoporosis leading to a risk of skeletal events. These skeletal events may have devastating impact on patient's quality of life due to bone pain, decreased performance and decreased mobility. They

may include vertebral fractures, vertebral collapse with spinal cord compression and peripheral fractures. The incidence of vertebral fractures has been reported as 15–30% per year, of peripheral fractures as 3–12% and up to 25% of patients are estimated to require radiotherapy for bone pain.[26] Biphosphonates have been introduced as long-term therapy to prevent skeletal complications. There is scarcity of placebo controlled data due to the rapid implementation of biphosphonates in routine clinical practice following clinical evidence from one randomised trial. In this trial a significant reduction of skeletal complications and a significant improvement in quality of life was reported after nine monthly infusions of intravenous pamidronate.[1] Overall, from available studies, the results of which have not always been confirmed in additional trials, it is estimated that biphosphonates can reduce the need for radiotherapy with 25% relatively, the occurrence of vertebral fractures with up to 41%, of non-vertebral fractures with up to 45% and of hypercalcaemia with up to 60%.[26]

In 2002, the American Society for Clinical Oncology (ASCO) guidelines on the role of biphosphonates in multiple myeloma were published. The guidelines recommend the use of intravenous pamidronate (90 mg) or intravenous zoledronic acid (4mg) every three or four weeks, in patients with lytic bone destruction on plain radiographs, patients with osteopenia and in patients with pain as adjunctive treatment to other therapies such as radiotherapy or surgery.[26] There is a lack of information to support recommendations with regard to the optimal duration of therapy. The guidelines suggest continuing treatment until there is evidence of substantial decline in the patient's general performance status. However, there are no criteria to establish the point at which patients no longer benefit from treatment and the decision to discontinue is generally empirical and based on personal experience.[26] Repeatedly, suggestions have been raised to a more efficient use of biphosphonates by individualisation of the need and dosing regimens based on markers of bone resorption. For example it has been suggested that in patients with complete remission following high-dose chemotherapy lower biphosphonate dosing regimens may be sufficient. There are however no clinical trial data to support these suggestion.[28] These individualised approaches may influence cost-effectiveness but to date no economic evidence is available.

At the time of the ASCO guidelines, no evidence was available to support the superiority of one agent over the other in reduction of skeletal events. However, zoledronic acid has been shown to be significantly more potent than pamidronate to normalise parameters of bone resorption and in the treatment of cancer related hypercalcaemia.[28] It has also been suggested to have a stronger direct cytotoxic antimyeloma effect than pamidronate.[29] To assess the clinical meaning of this antimyeloma effect, a phase III trial (Freund and Sezer) was set up in 2000 to establish whether zoledronic acid may prolong progression-free survival.[29] To date however, the choice to use either drug is attributed to their economic profile and centre preferences: although zoledronic acid is more costly to acquire, due to its shorter infusion time, total direct costs of treatment are quite similar (respectively US$ 728 and 726 for zoledronic acid and pamidronate). The longer infusion time for pamidronate versus zoledronic acid represents additional time lost for other activities, both to the patient, medical staff and the hospital. Costs associated with time lost are referred to as "opportunity costs". Additionally, the duration of infusion will have an impact on patient's quality of life. A time and motion study reported an average visit time of 1h 6 minutes versus 2h 52 minutes and a difference of 1.8 infusion chairs per day (DesHarnais in Ref. [27]).

A recent health economic comparison between pamidronate and zoledronic acid in metastatic breast cancer and multiple myeloma patients failed to report any preference from a health economic point of view.[2] This multinational prospective cost analysis in patients included in the large phase III trial comparing zoledronic acid with pamidronate reported no significant difference between therapies in terms of overall management costs: US$ 17958 for zoledronic acid versus US$ 15976 for pamidronate and no significant difference in the rate of skeletal events between treatments.

Although there is a lack of economic evidence, a number of parameters can logically be identified as drivers of costs: the time of therapy initiation, duration of treatment, route of administration and drug choice. Also, it has been suggested that cost reductions may be achieved by home infusion rather than clinic infusion of biphosphonates.[30] These parameters will influence the, likely important, economic impact of routine biphosphonate implementation in clinical practice. These costs are however to be balanced against important quality of life benefits through impact on pain, activity and performance status. In addition, they may be at least partially offset by savings from 25%–60% skeletal events avoided which contribute to financial burden from the associated hospitalisations for complications.[26] For example, a cost-benefit analysis with oral clodronate has suggested a 12% reduction in hospitalisation costs (28; Laakso, and Hillner in Ref. [26]). The four year costs of managing skeletal-related adverse events, including severe hypercalcaemia, vertebral and non-vertebral fractures, were calculated as € 1934 with clodronate therapy versus € 4109 in controls, representing a 50% cost reduction.[31] Despite these savings, the net cost increase from long-term clodronate has been reported between non-significant (Laakso in Ref. [31]) and € 4746, representing a 17% net cost increase.[31] Modelling studies and post hoc clinical trial based cost-effectiveness evaluations have reported that, to the Canadian or US healthcare system, intravenous pamidronate is associated with a net increase of total management costs.[26]

Preliminary cost-utility assessments in breast cancer patients have reported very conflicting results suggesting levels well above as well as within generally accepted ranges. To our knowledge no formal cost-utility analyses have been published in multiple myeloma. Given the relatively high cost of biphosphonate therapy and the long-term nature of treatment, it would be interesting to assess what the extent of benefit in terms of patient quality of life is and to compare the different available options. Additional research should therefore include utility assessments in patients with multiple myeloma receiving biphosphonate therapy as assessments of utility losses associated with myeloma related skeletal events such as peripheral fractures, vertebral fractures and spinal cord compression. Given the variability of possible presentations of skeletal events, it would require

quite large scale assessments to address the different possibilities. The availability of these utility values would at least enable to assess the cost-utility of compounds based on available clinical data through economic modelling. Such modelling would assist in estimating the potential impact of different dosing regimens, different treatment durations, and different indications (individualised treatments) on cost-utilities.

3.6. Novel therapeutic approaches

3.6.1. Bortezomib

The proteasome inhibitor Bortezomib is currently licensed for patients with refractory multiple myeloma. In this population it has been shown to increase median progression-free survival time by 2.1–3.3 months.[32] Evaluations are ongoing to assess the clinical benefits of using Bortezomib in different stages of the disease and in different combination regimens with other established multiple myeloma drugs such as dexamethasone, anthracyclines or alkylating agents, or together with established combinations such as VAD or AD.

Mehta[33] performed a cost-effectiveness analysis of Bortezomib in patients with advanced multiple myeloma in comparison to best supportive care + thalidomide. Different data sources were applied: phase II Bortezomib trial data, expert opinion analysis and literature review data. Bortezomib was concluded to provide the best value for money among approaches assessed. Given the relative weakness of underlying data it is preliminary to draw conclusions from this one assessment. No economic evaluations were identified related to its use in primary treatment. The need for formal economic evaluations, not only for Bortezomib but also for the other novel therapies, is however highlighted by reports mentioning the important cost difference between these therapies and standard, established drugs.[6] Although drug acquisition costs as such may provide some insight into the economic burden of these new therapies, the newest therapies may not yet have an official price and furthermore these prices are country-specific. Therefore, no acquisition costs are reported in this review.

3.6.2. Thalidomide

Thalidomide has been shown effective in the treatment of relapsed and refractory multiple myeloma. More recently, its use is being explored in previously untreated patients. In combination with dexamethasone it seems to show at least comparable and, in some studies, even improved response rates as compared to standard regimens such as VAD chemotherapy as initial therapy in ASCT candidates.[34] These findings led to the evaluation of the role of thalidomide in combination with pegylated liposomal doxorubicin, vincristine, and reduced-dose dexamethasone. This regimen was associated with response rates greater than 80% in patients with both newly diagnosed and relapsed/refractory multiple myeloma. Future applications of this and similar regimens for the treatment of multiple myeloma are currently being explored.

Through Medline search we were unable to identify any economic evaluation of thalidomide in the treatment of multiple myeloma.

3.6.3. Other IMIDS

Promising new classes of products under evaluation are the IMiDs, immunomodulating agents, functional analogues of thalidomide with potentially more potent anticancer activity and safety benefits over thalidomide. Also vaccination treatments are being subject of research for the management of multiple myeloma.

4. Discussion

Economic evidence in multiple myeloma is scarce. No recent cost-effectiveness evaluations were identified on therapy choices for induction chemotherapy. Inclusion of the new advances such as thalidomide or bortezomib in primary induction treatment may improve clinical outcomes as well as treatment costs. Economic evaluations would be valuable as additional information to assess the benefits of these potential new future regimens in primary induction.

High-dose chemotherapy with stem cell support has been shown cost-effective compared to conventional chemotherapy. Compared to high-dose chemotherapy alone, ASCT support may prove cost-effective when long-term benefits (>5 years) are considered. Long-term economic assessments are awaited.

Biphosphonates are considered cost-effective and have become part of routine practice since they significantly improve quality of life from preventing skeletal events. However, they are costly and no utility data are available to assess correctly the cost per QALY associated with these treatments. There is no evidence to support the choice of either pamidronate or zoledronic acid based on cost-utility or cost-effectiveness parameters. However, due to its practical benefit of shorter infusion time zoledronic acid is anticipated to have quality of life benefits and economic benefits and is therefore probably the more preferred option in clinical practice.

Total body irradiation has been largely abandoned since it increases costs as well as toxicity without clinical benefit.

Economic data on maintenance treatment with interferon-α currently do not support its use since cost-effectiveness ratios are generally beyond acceptability. This results from marginal improvements in progression-free survival without proven benefit on overall survival and an unfavourable impact of treatment on quality of life.

With regard to cost containment, in all stages and therapeutic classes of treatment (chemotherapy, biphosphonate therapy and transplantation), cost reductions can be achieved from increasing the use of outpatient rather than inpatient treatment administrations.

Economic literature with regard to the most recent advances in multiple myeloma is still largely lacking. Other gaps in current knowledge are related to quality of life assessments and more specifically utility assessments related to different disease states in multiple myeloma.

An important limitation of our study, especially with regard to novel therapeutic approaches such as thalidomide and bortezomib, is that we included only peer reviewed publications available on Medline. As a result, recent economic evaluations solely available as abstracts from presentations at congresses have not been included. The results of these analyses would be highly interesting, however, given the

limited information generally available from congress abstracts it is difficult to assess the quality hence weight of the evidence to assist clinical decision making.

Conflict of interest statement

None declared.

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